Characterizing the Autologous CD4bs Antibody Response in HIV-1 Clinical Trial Participants

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Background

In response to HIV infection, autologous antibodies (aAbs) develop, which target the envelope protein (Env). These antibodies are unable to clear the virus because Env is heavily glycosylated and tolerant of escape mutations. One HIV cure strategy is the administration of broadly neutralizing antibodies (bNAbs) which target conserved regions on the viral Env, such as the CD4 binding site (CD4bs). However, viral escape from bNAb treatment is still possible, and previous work suggests that the autologous response continues to drive viral selection but the consequence to bNAb resistance remains unknown[1]. Therefore, a better characterization of how the aAb response affects viral escape to bNAb therapy is needed.

Methods

Samples: IgG was purified from 35 total people living with HIV across three clinical trials. 13 of these individuals were from the A5340 clinical trial who received VRC01 before an analytical treatment interruption (ATI) from antiretrovirals (ARV). 22 of these individuals were from the VRC607 and VRC01 clinical trials who received VRC507-523 or VRC01 while viremic. All participants experienced viral rebound following bNAb administration.

Binding Assay: Four HIV proteins (gp120, gp41, RSC3, RSC3 Δ371I) were biotinylated and bound to a linker specific spot on an MSD multiplexed plate. Participant IgG was added at an initial concentration of 50 ug/mL and 5-fold serially diluted 7 times. Binding was measured by sulfo-tagged secondary antibodies specific to IgG subclasses 1-4. All values were corrected by subtracting the RLU of the average of the blank wells. Positivity for gp120 or gp41 autologous responses were defined as RLU values ≥100 at the highest Ig concentration. CD4bs responses were defined as a ≥4-fold difference between RSC3 and RSC3 Δ371I at the highest Ig concentration.

Statistics: Spearman correlations were calculated to determine if the strength of the CD4bs response was associated to the clinical outcomes of the administered bNAb in each clinical trial. Mann-Whitney T-tests were calculated to evaluate differences in IgG 1-4 levels between viremic and suppressed participants.

References

1. Klein F, Nogueira L, Nishimura Y, et al. Enhanced HIV-1 immunotherapy by commonly arising antibodies that target virus escape variants. J Exp Med. 2014 Nov 17;211(12):2361–72. PMCID: PMC4235636

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Results

Figure 1

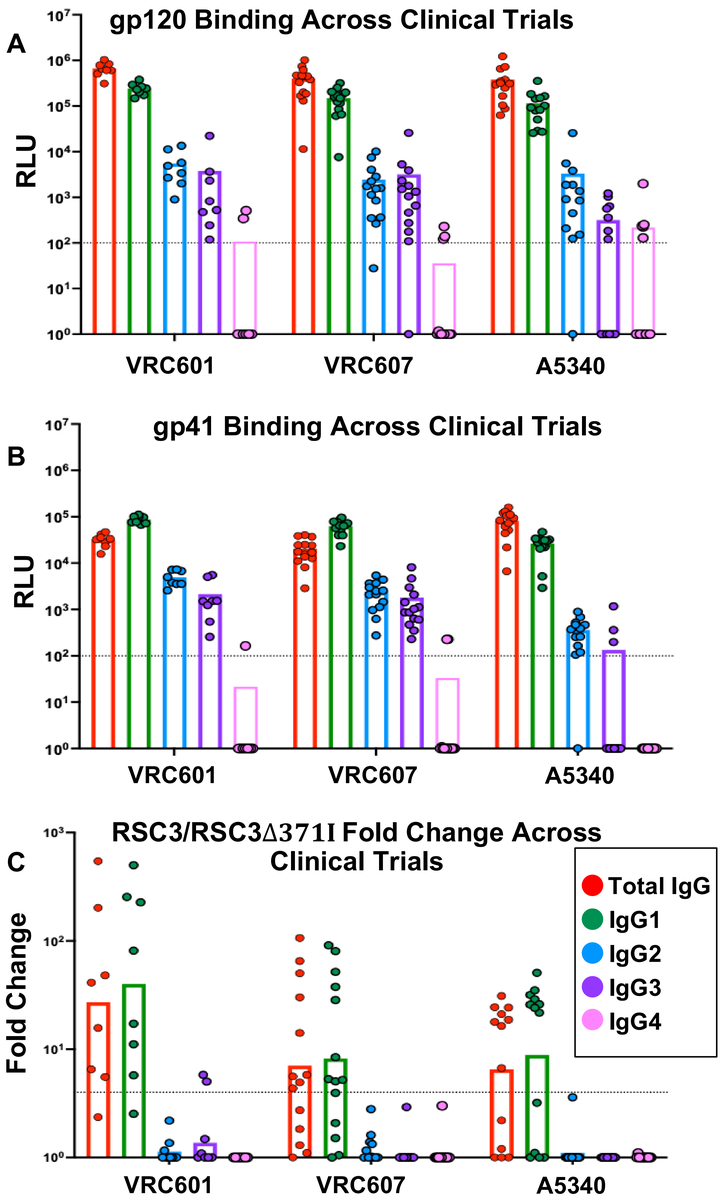


Figure 1. HIV-1–specific antibody subclass responses. (A) gp120-specific, **(B)** gp41-specific, and **(C)** CD4 binding site (CD4bs) directed antibody responses. All participants had detectable gp120 and gp41 responses, which were predominantly IgG1 and IgG2 subclasses. IgG3 responses differed by antiretroviral therapy (ART) status. IgG4 responses were infrequent. CD4bs-directed antibodies were detected in 25/35 participants (71%) and were predominantly IgG1.

Figure 2

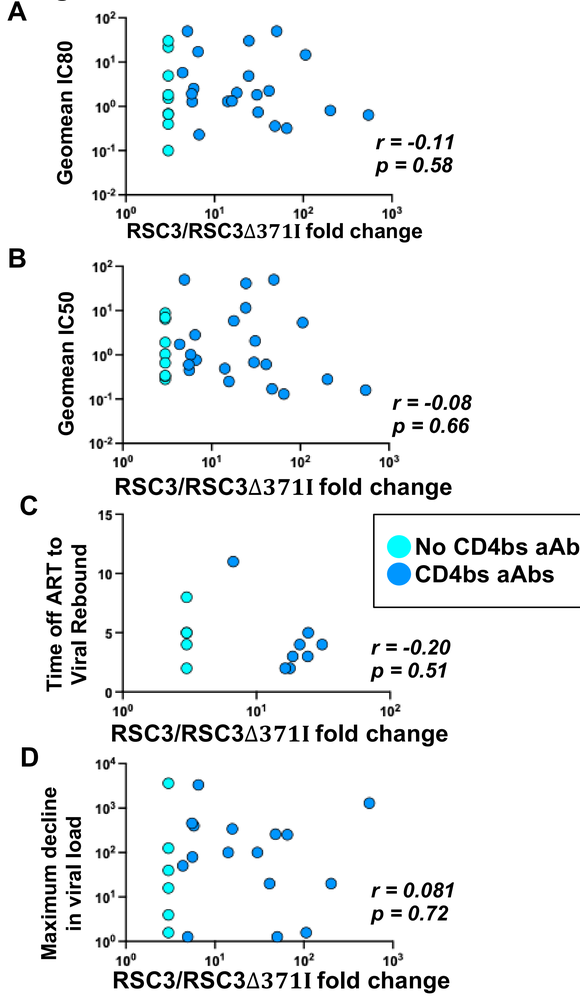


Figure 2. No detectable correlations between autologous CD4 binding site (CD4bs)–directed antibody responses and clinical outcomes following bNAb administration. CD4bs-directed IgG responses were measured by RSC3/RSC3 Δ371I binding and evaluated for associations with clinical outcomes in individuals with and without detectable CD4bs autologous antibodies using Spearman correlation analyses.

Figure 3

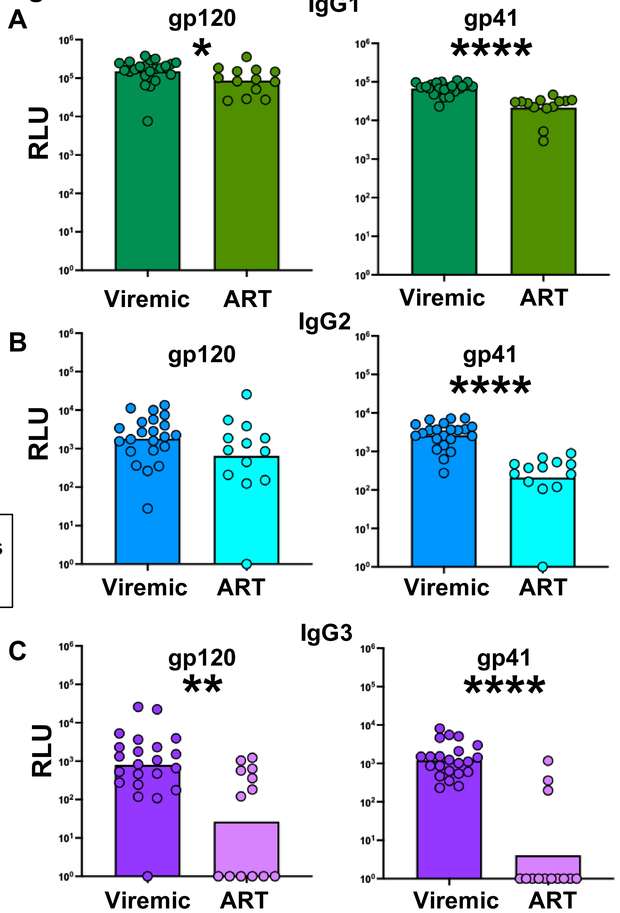


Figure 3. Differential IgG subclass responses to gp120 and gp41 in viremic versus ART-suppressed individuals. IgG subclass–specific antibody levels were measured in purified IgG from viremic and ART-suppressed individuals at 50 µg/ml against HIV-1 gp120 and gp41 antigens. Statistically significant differences were observed between viremic and ART-suppressed individuals for gp120 IgG1 ($p = 0.0178$; **A**) and IgG3 ($p = 0.0025$; **C**), but not IgG2 ($p = 0.1391$; **B**). In contrast, gp41-specific IgG subclass responses were significantly different between groups for all 3 subclasses ($p = 0.0001$ for each). Statistical comparisons were performed using Mann-Whitney T tests.

Conclusions

- All participants in these clinical trials had detectable gp120 and gp41 responses
- Autologous CD4bs antibodies are detectable in 71% of HIV clinical trial participants using our assay regardless of ART status
- There is not a detectable association between CD4bs autologous antibodies and CD4bs bNAb sensitivity using our current metrics for autologous CD4bs responses

Plain Language Summary

People living with HIV naturally make antibodies that recognize the virus. Here, we found that while these antibodies are common, their presence alone does not predict how well antibody interventions work, highlighting the need to better understand which immune responses work synergistically to control the disease.

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